Review

Efficacy of Colchicine in the Treatment of Patients With Coronary Artery Disease: A Mini-Review

JingWen Yong, MD[1,#]; JinFan Tian, PhD[1,#]; WenJian Jiang, PhD[2]; Xin Zhao, PhD[1]; HongJia Zhang, MD, PhD[2]; and XianTao Song, MD, PhD[1]

[1]Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; and [2]Department of Community Health Research, Beijing Institute of Heart Lung and Blood Vessel Disease, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

ABSTRACT

Purpose: This review of colchicine, an effective anti-inflammatory agent, examines whether the reduction in ischemic events produced by colchicine translates to a reduction in mortality, the optimal duration of treatment, and the patient populations that benefits the most from colchicine treatment.

Methods: We performed a comprehensive PubMed database search using the key words *colchicine* and *coronary heart disease* on August 23, 2021. We also screened the included reference list of manuscripts.

Findings: Colchicine's role in the secondary prevention of coronary artery disease has been the focus of recent large-scale randomized controlled trials in chronic coronary syndrome (ie, the Low-Dose Colchicine and Low-Dose Colchicine 2 trials), acute myocardial infarction (the Colchicine Cardiovascular Outcomes Trial and Colchicine in Patients With Acute Coronary Syndrome trial), and after percutaneous coronary intervention (the Colchicine–Percutaneous Coronary Intervention trial).

Implications: Current evidence suggests that low-dose colchicine (0.5 mg once a day) reduces the risk of cardiovascular events among patients with acute myocardial infarction or chronic coronary syndrome. Colchicine has the potential to become a new standard therapy for the prevention of coronary artery disease–related atherothrombotic events because it is effective and cost-efficient and has a well-tolerated safety profile. (*Clin Ther.* 2022;44:1150–1159.)

Key words: Anti-inflammatory, colchicine, coronary artery disease, treatment.

INTRODUCTION

Inflammation plays a central role in the pathogenesis and clinical manifestations of atherosclerosis.[1] The main mechanism of cardiovascular events is plaque activation and rupture, which can be promoted by enzymes and cytokines (ie, the interleukin [IL]-1β/IL-6 cytokine signaling pathway) that are released by inflammatory cells.[2] In the Canakinumab Anti-Inflammatory Thrombosis Outcome Study trial, specific IL-1β inhibition by canakinumab reduced the risk of cardiovascular events by 15% in 3 years (and did so in a lipid-level independent manner), further supporting inflammation's role in atherosclerosis.[3]

Colchicine is an anti-inflammatory agent with a wide range of properties. Its primary mechanism of action is the inhibition of tubulin polymerization and inactivation of the NLRP3 inflammasome (Figure 1).[4,5] In addition, recent basic research studies have found that colchicine can exert cardioprotective effects by modulating the nuclear factor–κB (NF-κB)/IκB axis.[6,7] Colchicine's tolerability and efficacy for reducing cardiovascular events have been assessed in several randomized controlled trials (RCTs) during the past decade.[8] Although pooled results have indicated that

[#]These authors contributed equally to this work.

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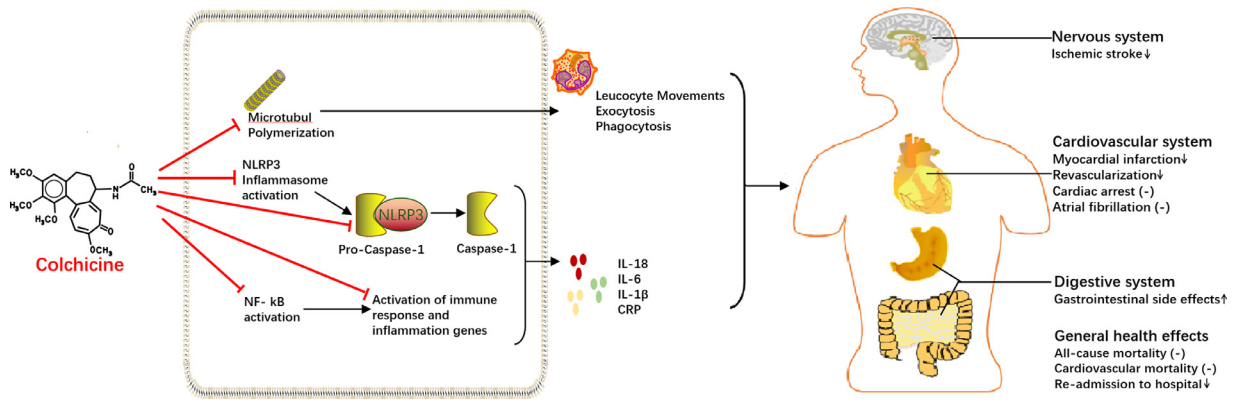

Figure 1. Anti-inflammatory mechanisms and clinical effects of colchicine on patients with coronary artery disease. The main anti-inflammatory pathways of colchicine include (1) inhibiting microtubule assembly, development, and elongation of microtubules; (2) inhibiting the activation of NLRP3 and caspase-1; (3) reducing the activity of the nuclear factor–κB complex; and (4) reducing immune responses and transcription of inflammatory genes. The red line refers to colchicine's inhibitory effects. CRP = C-reactive protein; IL = interleukin.

colchicine is not associated with a significant reduction in all-cause or cardiovascular mortality, it is correlated with reduced risks for myocardial infarction or stroke.[9] Nevertheless, several questions related to the treatment of coronary artery disease (CAD) with colchicine remain unanswered: Will the reduction in ischemic events translate to a reduction in mortality on longer-term follow-up? What is the optimal duration of treatment? Which patient populations can benefit the most from colchicine? The following summary addresses these outstanding questions.

Colchicine has a wide range of anti-inflammatory properties and has been used to treat gout, familial Mediterranean fever, and pericarditis.[10] Colchicine affects several inflammatory cell functions. It is involved in the recruitment, chemotaxis, and adhesion of neutrophils to damaged tissues[11] and inhibits leukocyte chemotaxis by changing their recruitment and adhesion on the surface of endothelial cells.[10] Colchicine has a therapeutic effect even at low doses because it is concentrated in endothelial cells and leukocytes and thus remains active for several days after administration.[5] Colchicine's antimitotic properties arise from its inhibition of tubulin polymerization (Figure 1), which results in reduced leukocyte movement, exocytosis, and phagocytosis.[12] The inhibition of tubulin also inhibits the expression of selectin in atherosclerosis, especially after myocardial infarction.[7]

Colchicine also protects the cardiovascular system by inhibiting NF-κB complex activity, which subsequently suppresses immune responses and the activation of inflammasome genes.[6,13] Recently, Cirillo et al[6] found that colchicine prevents tissue factor expression in oxidized low-density lipoprotein–stimulated T cells by modulating the NF-κB/IκB axis. They also found that colchicine inhibits the prothrombotic activity of oxidized low-density lipoprotein by modulating the NF-κB/IκB pathway, which has beneficial cardiovascular effects.[7]

Colchicine can also inactivate the NLRP3 inflammasome, which reduces the release of the proinflammatory cytokines IL-1β, IL-18, IL-6, and C-reactive protein (CRP).[4,5] Robertson et al[4] found that acute colchicine treatment after acute coronary syndrome (ACS) significantly reduced the level of caspase-1 messenger RNA transcription and protein secretion, which in turn reduced monocyte-secreted IL-1β levels in patients with ACS patients with myocardial infarctions.

However, a 2001 pilot trial on the effect of colchicine compared with placebo on high-sensitivity C-reactive protein in patients with ACS or acute stroke (COOL trial), the 2017 Interest of Colchicine in the Treatment of Patients With Acute Myocardial Infarction and With Inflammatory Response (COLIN) study, and the 2019 Low-Dose Colchicine After Myocardial Infarction (LoDoCo-MI) trial all found that the CRP levels were

not that different in patients with ACS in a control group and patients with ACS in a colchicine treatment group.[14–16] Thus, early use of colchicine appears to not completely inhibit inflammatory responses in patients with ACS or acute ischemic stroke.

Chronic Coronary Syndrome

Colchicine reduces cardiovascular events in patients with chronic coronary syndrome (CCS) in multiple RCTs (Table I), including the 2013 LoDoCo trial and the 2020 LoDoCo2 trial.[18,25] However, colchicine did not reduce cardiovascular mortality and was correlated with a mild increase in noncardiovascular mortality.[18]

The LoDoCo trial found that adding 0.5 mg/d colchicine to the standard medical treatment of patients with CCS significantly reduced the risk of cardiovascular events (including ACS, out-of-hospital cardiac arrests, and noncardiac ischemic strokes).[25] Colchicine may help prevent cardiovascular events caused by inherent atherosclerotic plaque instability in patients with CCS by inhibiting the inflammatory responses that have been established in unstable coronary plaques. The much larger LoDoCo2 study (which included 5522 patients) also reported that colchicine could reduce the risk of cardiovascular events in patients with CCS, which was mainly attributed to the reduction in ACS unrelated to stent disease.[18] In addition, the 2021 LoDoCo2 trial compared the end point of major adverse cardiovascular events between patients without previous ACS and those who had prior ACS at different time points and found that colchicine's benefits were independent of both the incidence and timing of prior ACS.[19]

However, compared with placebos, the number of noncardiovascular deaths in patients treated with colchicine was higher in the LoDoCo2 trial (hazard ratio = 1.51; 95% CI, 0.99–2.31).[18] A smaller Australian study of 795 patients also found that the number of noncardiovascular deaths in patients treated with colchicine was higher (hazard ratio = 8.20; 95% CI, 1.03–65.61).[20] A recent meta-analysis and review compiled the main outcome of noncardiovascular deaths of all notable studies to date and found a trend of higher noncardiovascular mortality in patients treated with colchicine.[8,9,21]

Acute Coronary Syndrome

Since 2011, a total of 5 RCTs have analyzed the efficacy of colchicine for patients with ACS with varying results (Table I). The COOL trial found that, in 80 patients, 30 days of 1 mg of colchicine did not inhibit inflammation, as measured by serum CRP, in patients with ACS or acute ischemic stroke.[14] Furthermore, the COLIN study and the 2019 LoDoCo-MI study had similar results.[15,16] The 2019 Colchicine Cardiovascular Outcomes Trial was a double-blind RCT of 4745 patients with acute myocardial infarction within 30 days that found that low-dose colchicine can reduce the risk of subsequent ischemic stroke and angina (which can lead to emergency hospitalization for revascularization), but myocardial infarction, cardiac death, and all-cause death were not reduced.[23,24,26] In addition, Deftereos et al[30] found that, in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary interventions (PCIs), colchicine treatment could reduce infarct size (as defined by biomarker release and scar assessment with late-gadolinium enhancement on cardiac magnetic resonance imaging). However, the Colchicine in Patients With Acute Coronary Syndrome study did not find any cardiovascular benefits of adding colchicine to standard drug treatments after ACS. Instead, colchicine therapy was associated with higher noncardiovascular mortality.[20]

Revascularization Therapy

ACS is characterized by plaque rupture, ulcer, erosion, and/or calcified nodules. All the current methods used for percutaneous coronary revascularization cause mechanical damage to the coronary vascular system, resulting in increased local IL-6 release and neutrophil adhesion. The subsequent inflammatory reaction involves endothelial hyperplasia, which leads to significant restenosis.[2] Colchicine can reduce coronary microcirculation disturbance, improve endothelial function, and reduce subsequent myocardial injury and major adverse cardiovascular events. It can also curb in-stent restenosis by changing the formation of new atherosclerosis through dampening the acute inflammation caused by ACS and/or PCI.[12] Several medium-sized trials have evaluated the efficacy of colchicine in patients requiring coronary revascularization (Table II).

ROLE OF COLCHICINE IN PCI

The LoDoCo study found that colchicine was associated with a reduced risk of cardiovascular events

Table I. Summary of the colchicine study population for different types of CAD.

Study	Study Year	Location	No. of Patients	Type of CAD	Study Design	Colchicine Dose	Outcomes*	Follow-up Time
CCS								
LoDoCo2 [18,19]	2020	Multinational/ multicenter	5522 (2762/2760)	CCS	Double-blind, placebo-controlled RCT (2:1 fashion)	0.5 mg Once a day	Cardiovascular death (−); new MI↓; ischemic stroke (−); ischemia-driven revascularization↓; DVT/PE (−); all-cause mortality (−)	28.6 mo
LoDoCo[25]	2013	Australia/ single center	532 (282/250)	CCS	RCT, prospective, observer-blinded end point (standard therapy)	0.5 mg Once a day	Primary outcome↓: ACS, out-of-hospital cardiac arrest, or ischemic stroke; new MI↓; unstable angina↓; cardiac arrest (−); stroke (−)	36 mo
ACS								
COPS[20]	2020	Australia/ multicenter	795 (396/399)	ACS	Double-blind, placebo-controlled RCT (2:1 fashion)	1 month 0.5 mg BID; then 0.5 mg Once a day	Primary outcome (−): all-cause mortality, new ACS, ischemia-driven urgent revascularization, and noncardioembolic stroke; all-cause mortality↑; cardiovascular mortality (−); new ACS/MI (−); stroke (−); ischemia-driven revascularization↓; hospitalization for chest pain (−)	400 d

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Table I. (*continued*)

Study	Study Year	Location	No. of Patients	Type of CAD	Study Design	Colchicine Dose	Outcomes*	Follow-up Time
LoDoCo-MI[16]	2019	Australia/ single center	237 (119/118)	AMI	Double-blind, placebo-controlled RCT (1:1 fashion)	0.5 mg Once a day	Residual CRP ≥2 mg/L at 30 d (−); CRP levels (−); therapy adherence (−); adverse events (−); readmission to hospital↓	30 d
COLCOT[23,24,26]	2019	Multinational/ multicenter	4745 (2366/2379)	AMI	Double-blind, placebo-controlled RCT (1:1 fashion)	0.5 mg Once a day	Cardiovascular mortality (−); cardiac arrest (−); MI (−); stroke↓; revascularization↓; all-cause mortality (−); atrial fibrillation (−); DVT/PE (−)	22.6 mo
Robertson et al[4]	2016	Australia/ single center	20 (9/11)	ACS	Double-blind, placebo-controlled RCT (1:1 fashion)	1 mg followed by 0.5 mg 1h later	IL-1β↓; procaspase-1 mRNA↓; caspase-1 protein↓	2 d
COOL[14]	2011	Canada/ single center	80 (40/40)	ACS	Double-blind, placebo-controlled RCT (1:1 fashion)	1 mg Once a day	hs-CRP level at 30 d (−); platelet function (−)	1 mo
CAD								
Kajikawa et al[17]	2019	Japan/2 centers	28 (14/14)	CAD	Double-blind, placebo-controlled, crossover RCT (1:1 fashion)	0.5 mg Once a day	FMD (−); serum concentrations of hs-CRP↓	14 d

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Table I. (*continued*)

Study	Study Year	Location	No. of Patients	Type of CAD	Study Design	Colchicine Dose	Outcomes*	Follow-up Time
Martínez et al[22]	2015	Australia/ single center	73 (34/39)	ACS/ CCS/ controls	Double-blind, placebo-controlled RCT (1:1 fashion)	1 mg followed by 0.5 mg 1 h later	IL-1β↓; IL-18↓; IL-6 concentrations↓	1 d

ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; CCS = chronic coronary syndrome; COOL = pilot trial on the effect of colchicine compared with placebo on high-sensitivity C-reactive protein in patients with ACS or acute stroke; COPS = Colchicine in Patients With Acute Coronary Syndrome; DVT/PE = deep vein thrombosis/pulmonary embolism; FMD = flow-mediated vasodilation; hs-CRP = high-sensitivity C-reactive protein; IL = interleukin; LoDoCo = Low-Dose Colchicine; MI = myocardial infarction; mRNA = messenger RNA; RCT = randomized controlled trial.

*Minus sign indicates was no statistical difference; downward arrow, colchicine reduced the result, which was statistically significant; upward arrow, colchicine increased the result, which was statistically significant.

and that the risk continued to decrease over time, largely because of subsequent ACS unrelated to the initial stent.[25] These results suggest that colchicine may be ineffective in preventing stent-related complications and that its role is more pronounced in preventing cardiovascular events caused by atherosclerotic plaque instability in patients with CCS (possibly by inhibiting inflammatory pathways that have been identified in unstable coronary plaques). O'Keefe et al[27] compared restenosis rates 6 months after coronary angioplasty in 197 patients with CAD back in 1992 and found that colchicine did not reduce the incidence of stent restenosis (46% versus 47%, P = nonsignificant).

In contrast, Deftereos et al[31] randomized 196 patients with diabetes undergoing PCI treatment with bare metal stents to receive 0.5 mg of colchicine twice daily (started within 24 hours after PCI) or a placebo for 6 months. The study found that at 6 months the rates of stent restenosis angiography in the colchicine group and the control group were 16% and 33%, respectively (odd ratio 0.38; 95% CI, 0.18–0.79; $P = 0.007$). Intravascular ultrasonography found that, compared with placebo group, the volume of neointima in the colchicine group was reduced by 70% ($P < 0.01$). Although limited by sample size, this trial found that colchicine treatment in patients with diabetes potentially reduced in-stent restenosis.

Whether colchicine can reduce PCI-related myocardial damage is also controversial. In the Colchicine in Percutaneous Coronary Intervention (COLCHICINE-PCI) trial, 400 individuals undergoing PCI were randomly assigned to receive 1.8 mg of preprocedural colchicine or a corresponding placebo. The study found that colchicine significantly reduced IL-6 and high-sensitivity CRP concentrations 22 to 24 hours after PCI. The colchicine group also had a numerical reduction in PCI-related myocardial damage, but this difference was not statistically significant (57.3% in the colchicine group and 64.2% in the placebo group, $P = 0.19$). This finding is consistent with the trial results in patients with CCS and ACS.[28] However, the 2015 study by Deftereos et al[30] found that in patients with STEMI undergoing primary PCI, colchicine treatment could reduce infarct size and the extent of myocardial damage (as assessed by cardiac biomarkers and late gadolinium enhancement on magnetic resonance imaging). The Colchicine-PCI trial included elective procedures, whereas the study by Deftereos et al[30] only included STEMI, which could potentially account for the difference in results. In summary, the benefits of the short-term use of colchicine to reduce myocardial injury during the periprocedural period for patients undergoing PCI remain to be elucidated, and further research

Table II. Summary of colchicine study population undergoing revascularization.

Study	Study Year	Location	No. of Patients	Type of CAD	Study Design	Colchicine Dose	Outcomes*	Follow-up Time
COLCHICINE-PCI[28]	2020	US/single center	400 (206/194)	CAD undergoing PCI	Double-blind, placebo-controlled RCT (1:1 fashion)	1.8 mg before procedure followed by 0.6 mg Once a day	PCI-related myocardial injury (−); all-cause mortality (−); (nonfatal) new MI (−); target vessel revascularization (−); PCI-related MI (−); change in IL-6↓, IL-1β↓, and CRP levels↓	1 mo
COLIN[15]	2017	France/ single center	45 (23/22)	STEMI undergoing PCI	RCT, prospective, open-label trial, standard therapy	1 mg Once a day	CRP peak value in-hospital (−); peak hs-TnT level (−); major adverse cardiac events (−); cardiac remodeling on CMR↑	1 mp
Zarpelon et al[33]	2016	Brazil/ single center	140 (71/69)	AF, CCS undergoing CABG	RCT, prospective, open-label trial standard therapy	1.0 mg (loading dose) before CABG 0.5 mg BID until discharge	Postoperative atrial fibrillation (−); all-cause mortality (−); length of hospital stay (−); postoperative infections↑	Mean (SD) in-hospital, 14.5 (11.5) d
Giannopoulos et al[29]	2015	Greece/ single center	59 (30/29)	CCS undergoing CABG	Double-blind, placebo-controlled RCT (1:1 fashion)	0.5 mg BID	Peak hs-TnT level (within 48 h after CABG)↓; peak CK-MB level↓; AUC of CK-MB and hs-TnT	10 d
Deftereos et al[30]	2015	Greece/ multicenter	151 (77/74)	STEMI undergoing PCI	Double-blind, placebo-controlled RCT (1:1 fashion)	2.0 mg (loading dose) 0.5 mg BID	AUC of CK-MB↓; peak hs-TnT level↓; absolute MI volume by CMR↓; all-cause mortality (−)	5 d

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Table II. (*continued*)

Study	Study Year	Location	No. of Patients	Type of CAD	Study Design	Colchicine Dose	Outcomes*	Follow-up Time
Deftereos et al[31]	2013	Greece/ single center	196 (100/96)	CAD undergoing PCI with BMS (DM)	Double-blind, placebo-controlled RCT (randomization in 1:1 fashion)	0.5 mg BID	In-stent restenosis↓; parameters of lumen loss↓	6 m
O'Keefe et al[27]	1992	US/single center	197 (130/67)	CAD undergoing PCI with BMS	Double-blind, placebo-controlled RCT (randomization in 2:1 fashion)	0.6 mg BID	All-cause mortality (−); recurrent ischemia (assessed by MIBI thallium scan) (−); angiographic restenosis (−)	6 m

BMS = bare-metal stent; CABG = coronary artery bypass graft; CAD = coronary artery diseases; CCS = chronic coronary syndrome; COLCHICINE-PCI = Colchicine–Percutaneous Coronary Intervention; CMR = cardiovascular magnetic resonance; COLIN = Interest of Colchicine in the Treatment of Patients With Acute Myocardial Infarction and With Inflammatory Response; CRP = C-reactive protein; hs-TnT = high-sensitivity troponin T; LD = low dose; IL = interleukin; MI = myocardial infarction; MIBI = dipyridamole/technetium sestamibi; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; STEMI = ST-segment elevation myocardial infarction.

*Minus sign indicates was no statistical difference; downward arrow, colchicine reduced the result, which was statistically significant; upward arrow, colchicine increased the result, which was statistically significant.

determining its utility for stent restenosis needs to be conducted.

ROLE OF COLCHICINE IN CORONARY ARTERY BYPASS GRAFT SURGERY

Giannopoulos et al[29] conducted a double-blind, placebo-controlled RCT in 2015, enrolling 59 patients undergoing CABG. Colchicine 0.5 mg was taken twice daily beginning 48 hours before the operation and continued for the 8 days after the operation. Compared with a placebo, short-term perioperative colchicine treatment was found to effectively reduce the increase in high-sensitivity troponin T and creatine kinase MB after coronary artery bypass graft procedures.

The Colchicine for the Prevention of the Postpericardiotomy Syndrome substudy published by Imazio et al[32] provided some insights into whether colchicine could reduce atrial fibrillation rates after cardiac surgery. In 426 patients undergoing cardiac surgery involving pericardiotomy, 1 month of postoperative colchicine therapy reduced the incidence of atrial fibrillation from 22% to 12% ($P = 0.021$ compared with a placebo group). The lengths of hospitalization ($P = 0.04$) and recovery time ($P = 0.009$) were also shortened. However, in this study, colchicine began the third day after surgery, and the highest incidence of atrial fibrillation occurred in the first 2 to 3 days after pericardiotomy.[33]

In contrast, Zarpelon et al[33] found that colchicine was not effective in preventing atrial fibrillation after myocardial revascularization surgery (colchicine versus control group: 7.04% vs. 13.04%, $P = 0.271$) in 140

patients. There were also no mortality (5.6% versus 10.1%; $P = 0.363$) or length of hospital stay (mean [SD], 14.5 [11.5] versus 13.3 [9.4] days; $P = 0.490$) benefits identified.

CONCLUSION

Colchicine is a cost-efficient anti-inflammatory agent with a good safety profile that is effective in reducing adverse cardiovascular events in patients with CAD. For patients with recent myocardial infarction or CCS, long-term colchicine treatment at a dose of 0.5 mg/d can be considered to improve nonfatal cardiovascular outcomes. In patients undergoing PCI, early postprocedural colchicine treatment can reduce myocardial damage, but its benefit in reducing in-stent restenosis still needs to be determined. We look forward to the results of the ongoing Colchicine and Spironolactone in Patients with ST Elevation MI and SYNERGY Stent Registry and the Colchicine for Prevention of Vascular Inflammation in Non-Cardioembolic Stroke trials to provide us with further answers on this topic.

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AUTHOR'S CONTRIBUTION

Xiantao Song and HongJia Zhang helped to conceive the theme and revise the manuscript. Jingwen Yong and Jinfan Tian participated in the research selection, data extraction and manuscript drafting. Xin Zhao and Wenjian Jiang contributed data collation and manuscript revision. Funding sources had no involvement.

DATA AVAILABILITY

All data included in this study are available upon request by contact with the corresponding author.

DECLARATION OF INTEREST

None declared.

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Address correspondence to: HongJia Zhang, PhD, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Chaoyang District, Anzhen Road No. 2, Beijing City 100029, China E-mails: zhanghongjia722@ccmu.edu.cn.
XianTao Song, MD, PhD, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Chaoyang District, Anzhen Road No. 2, Beijing City 100029, China. E-mails: zhanghongjia722@ccmu.edu.cn.